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09/032,972	02/26/1998	ACHIM H. KROTZ	ISIS-2710	1518

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CRANE, LAWRENCE E

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1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/032,972	Applicant(s) Krotz et al.	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE --3-- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communication(s) filed on -10/09/01 (amdt D & IDS)-.
[] This action is **FINAL.**
[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims ---1-42--- are pending in the application. Claims -[]- have been cancelled.
Of the above claim(s) ---[]--- is/are withdrawn from consideration.
[] Claim(s) ---[]--- is/are allowed.
[X] Claims ---1-42--- are rejected.
[] Claim(s) ---[]--- is/are objected to.
[] Claim(s) ---[]--- are subject to restriction or election requirement.

Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
[] The proposed drawing correction, filed on -[]- is [] approved [] disapproved.
[] The drawing(s) filed on -[]- is/are objected to by the Examiner.
[] The specification is objected to by the Examiner.
[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
[] All [] Some* [] None of the CERTIFIED copies of the priority documents have been
[] received.
[] received in Application No. (Series Code/Serial Number) -[]-.
[] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: -[]-.

Attachment(s)

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). --23--
[X] Notice of Reference(s) Cited, PTO-892
[] Notice of Draftsperson's Patent Drawing Review, PTO-948
[] Interview Summary, PTO-413
[] Notice of Informal Patent Application, PTO-152
[] Other: -[]-.

No claims have been cancelled, claims **1 and 21** have been amended, and new claim **42** has been added as per the amendment filed October 9, 2001. Also, an Information Disclosure Statement (IDS) filed October 9, 2001 has been received with one cited reference and made of record.

Claims **1-42** remain in the case.

Claim **42** is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **42**, the term "DCA" is apparently an acronym (dichloroacetic acid?). Applicant is respectfully requested to make explicit what chemical compound (complete name) is being identified followed by the acronym {e.g. -- dimethyl formamide (DMF) --} at the first occurrence to insure clarity.

Applicant's arguments with respect to claims **1-41** have been considered but are moot in view of the new grounds of rejection.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **1-42** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Ravikumar '621** (PTO-892 ref. **A**) in view of **Caruthers et al. '679** (PTO-892 ref. **G**) and further in view of

Froehler et al. '076 (PTO-892 ref. **H**) and further in view of **Sproat et al.(I)** (PTO-892 ref. **W**), **Conway et al.** (PTO-892 ref. **Y**), **Atkinson et al.** (PTO-892 ref. **Z**), and **Sproat et al.(II)** (PTO-892 ref. **RA**).

The instant claims are directed to entirely conventional, 7 step oligonucleotide syntheses conducted using an automated device to execute steps 2-6 {aka steps b) through f)}, wherein the only variation from the prior art is the choice of solvent or solvent mixture present for deprotection step (c).

Ravikumar '621 (PTO-892 ref. **A**) discloses entirely conventional oligonucleotide synthesis wherein the solvent for the coupling step is acetonitrile in the examples and the P-protecting group varies from the conventional phosphorus-ester protecting group. At column 3 this reference refers to several different patents which disclose the solid phase synthesis of oligonucleotides including three Caruthers et al. patents now cited herein as PTO-892 references **I, J and K**. Each of these Caruthers et al. patents discloses the automation of the synthesis of oligonucleotides via process steps closely analogous to, if not identical with, the process steps claimed herein, the most detailed disclosure occurring in Caruthers et al. '418 (PTO-892 ref. **K**). In the Ravikumar '621 patent at column 10, lines 1-16, a generic disclosure of the process steps leading to an oligonucleotide is presented, including acid-mediated deprotection of the 5'-hydroxyl moiety of a solid-support-attached nucleoside. However, no disclosure of any preferred solvent for the required acid reagent is included. In the same column at line 50, the removal of 5'-hydroxyl protection by contact with acid from a solid-support-attached oligonucleotide is also taught without specifying any particular solvent. At column 14, lines 5-28, a more complete disclosure of possible 5'-hydroxyl protecting groups is provides along with a list of acids effect to deprotect, but no preferred solvents are

listed. At column 18, lines 37-41, deprotection is accomplished by contact with a solution of dichloroacetic acid in dichloromethane, conditions repeated in subsequent experimental procedures. The choice of any particular deprotection solvent is therefore apparently a choice within the purview of the ordinary practitioner in view of this disclosure. This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Caruthers et al. '679 (PTO-892 ref. **G**) at column 5, lines 10-14, teaches the use of "... any solvent which will dissolve the reactants ..." including a list of specific organic solvents for phosphoramidite-intermediate-based oligonucleotide synthesis. The context of this statement suggests that Caruthers was making reference to the coupling step. However, the same generic teaching appears to also apply to the deprotection step where four different solvent/reagent systems were disclosed by Caruthers as effective in the 5'-O-detritylation process:
(1) see column 16, Table IV, footnote 1 ($ZnBr_2$ in nitromethane);
(2) see column 16, Table V, footnote 1 (toluenesulfonic acid in chloroform:methanol (7:3));
(3) see column 18, lines 26-28 ($ZnBr_2$ in nitromethane:methanol (19:1)); and
(4) see column 19, lines 47-50 (80% acetic acid).
This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Froehler et al. '076 (PTO-892 ref. **H**) discloses the use of H-phosphonate intermediates for the coupling step in the synthesis of oligonucleotides and phosphorothioate analogues thereof, including reference to the automated synthesis thereof using a "Biosearch Model 8600 DNA synthesizer" at column 9, lines 22-23. This reference also teaches the use of " ... an anhydrous organic solvent, preferably

pyridine/acetonitrile ...," at column 5, lines 26-28. This "what ever works best" philosophy apparently also applies to the deprotection step; see column 5, lines 38-47. The last line of this portion of column 5 is particularly instructive. After listing 3 (three) different deprotection reagent/solvent mixtures, Froehler suggests a very flexible "whatever works" approach by further stating that "[o]ther deprotection procedures suitable for other known protecting groups will be apparent to the ordinary practitioner." This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Sproat et al.(I) (PTO-892 ref. **W**) discloses at p. 52, (lines 2 and 18) that toluene is useful for the purification of synthetic nucleoside intermediates. Additionally, this reference discloses at pp. 64 (Protocol 17, step 3) and page 70 (Protocol 25, step 4) that benzene is a solvent for key oligonucleotide synthesis reagents and for nucleoside-3'-O-phosphoramidites, and may be used to co-evaporate triethylamine therefrom.

Conway et al. (PTO-892 ref. **Y**) is directed to the chemical synthesis of labeled DNA and at p. 218, Section C, Subsection 2, discloses the specific use of toluene as an effective solvent for dissolution of pyridine-contaminated dinucleoside monophosphorothioate d[Cp(s)C] prior to co-evaporative removal of the pyridine/toluene mixture therefrom. The instant reference does not disclose that toluene is used in the coupling step required to make this compound.

Atkinson et al. (PTO-892 ref. **Z**) discloses at p. 43 in section (xvii), that toluene is useful to dissolve the 3'-O-phosphoramidites of 2'-deoxyadenosine, 2'-deoxycytidine, and 2'-deoxyuridine as the first step

in a re-precipitation or recrystallization process. This reference also teaches at p. 76, section 7.5, "Variation in Procedures," although no specific teaching of the substitution of an aromatic solvent from other solvents used in oligonucleotide synthesis is present in this section. In section 8.7 at p. 80, "toluene" is listed as a reagent useful in the preparation of "Deoxyribonucleoside-derivatized supports." This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

Sproat et al.(II) (PTO-892 ref. **RA**).at p. 84, lines 10 and 9 from the end of the page, discloses that the "[p]urity of solvents and reagents is of the utmost importance as far as reliability and reproducibility of the [oligonucleotide synthetic] method are concerned." This reference also discloses at p. 93, section (xv), that a di-protected adenosine derivative may be effectively dissolved in toluene prior to evaporative solvent removal for the purpose of co-evaporating residues of pyridine therefrom (see also p. 96, section (vi) for a similar disclosure). Additionally, at p. 111, section 7.6, the listing of solvents useful in oligonucleotide synthesis includes both benzene and toluene. This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

The teachings of the prior art Caruthers '679 and Froehler '076 references motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation. The first three references (**A, G and H**) and the additional Caruthers et al. patents cited by Ravikumar et al.'621 provide descriptions of conventional prior art processes for making oligonucleotides via phosphoramidite or H-

phosphonate intermediates, including the 5'-O-deprotection process step and including details of how the process has been automated in **H** and by patents cited in **A**. The noted portions of the Caruthers '679 and Froehler '076 both teach that the choice of a particular solvent or solvent mixture is a variable clearly within the purview of the ordinary practitioner. The Sproat et al.(I) (**W**), Conway et al., Atkinson et al., and Sproat et al.(II)(**RA**) references are each generally directed to oligonucleotide synthesis thereby providing proper motivation to combine with the primary references. The secondary references provide disclosures that at least two different nucleoside-3'-O-phosphoramidites, at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene. These disclosures are deemed to provide factually specific motivations for the ordinary practitioner conducting routine experimentation to substitute toluene, benzene, or their closely related aromatic solvent relatives as substitutes for at least a portion of the solvents typically used during the deprotection step in oligonucleotide synthesis. For these reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed October 3, 2001 have been fully considered but they are not persuasive.

Applicant disagrees with the instant grounds of rejection apparently on the basis that the prior art does not grant the ordinary practitioner wide latitude in the selection of a solvent, arguing that "[a]pplicants

disagree that the disclosure of solubility of the nucleosidic species recited by the Office Action motivate the use of Applicants' claimed deprotection solvent." Examiner disagrees with the assertion because the motivation to combine resides in the primary references, while the secondary references merely provide prior art wherein lists of solvents useful in oligonucleotide synthesis are provided, and therefore would be both known and readily accessible to the ordinary practitioner seeking to optimize the prior art. Examiner also notes in this non-final action that applicant has provided a reference wherein a deprotection solvent/reagent mixture is disclosed which reads directly on the instant claims (Horn et al., PTO-1449 ref. **CB**), clear evidence that not all practitioners in the instant art are wedded to the protocols provided by oligonucleotide synthesis apparatus manufacturers.

Applicant then argues that "there is no motivation to the art skilled to change those [manufacturer specified] conditions to achieve Applicants' claimed invention." Examiner respectfully disagrees with this position, because the prior art as recited on PTO-1449's and PTO-892's extends well beyond the instruction manuals for DNA synthesis machines, and notes also that no DNA synthesis machine manuals appear to have been made of record either by Examiner or Applicant's.

Applicant's then argue that " ...there is no motivation in the cited prior art ... to modify the teaching of the cited art (i.e. customary oligonucleotide synthesis protocols) to achieve Applicant's claimed invention." Examiner respectfully disagrees, noting again that the primary references leave open the selection of solvents for each and every particular step to the ordinary practitioner, a clear motivation to pick any solvent so long as it does not participate in the reaction to produce an undesired side reaction.

Applicant then argues that "what is required is a a teaching motivating the use of the claimed deprotection solvents," and then argues that the instant Office action is arguing in support of an "obvious to try" standard, citing *In re O'Farrell.* Examiner respectfully disagrees. Applicant's argument appears to suggest that the "obvious to try" standard renders all routine experimentation out of bounds, and therefore that patent protection afforded to Caruthers and Froehler only covers the specific embodiments disclosed in the cited patents. It seems to Examiner that this view is inconsistent with other decisions, noting in particular the guidance that "obvious to try" is not a valid test of patentability according to *In re Dow Chemical Co.* (CAFC 1988) at 5 USPQ2d 1276.

And lastly, applicant's disclosed embodiments do not appear to have solved any particular problem in oligonucleotide synthesis, or otherwise generated any basis for an allegation of unexpected results. In support of this view Examiner notes that a process which is directed to a selection of variables within the broad teaching of the prior art is not patentable if the results achieved vary merely in degree from that obtained in the prior art according to *In re Reven* (CCPA 1968) at 156 USPQ 679.

For the above reasons the instant grounds of rejection have been maintained.

Claims **1-42** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Horn et al.** (PTO-1449 ref. **CB**) in view of **Horn et al.** (PTO-892 ref. **VA**) as described in reference **CB** at page 6965, first full paragraph (citation "(2)").

The instant claims are directed to a standard 7 step synthesis of oligonucleotides and analogues thereof wherein the variation from standard procedure is the use of an aromatic solvent, in particular toluene, as the solvent for the protic acid reagent in the deprotection step.

Horn et al.(CB) discloses the use of dichloroacetic acid in toluene for the trityl deprotection step in the synthesis of oligonucleotides. Horn notes in particular that a higher than usual (for single deprotection) concentration of dichloroacetic acid effects rapid de-tritylation when multiple de-tritylations must be conducted simultaneously in the parallel extensions of separate oligonucleotide chains is required for the synthesis of multiply branched oligonucleotide "fork and comb" type probes.

According to **Horn et al.(CB)**, **Horn et al.(UA)** discloses further details relevant to the application of dichloroacetic acid/toluene mixtures in de-tritylation of 5'-tritylated oligonucleotide precursors during single and multiple/simultaneous synthetic oligonucleotide chain extension(s).

The prior disclosure of a standard phosphoramidite-type oligonucleotide synthesis wherein the de-tritylation step relies on a mixture of dichloroacetic acid and toluene is deemed to be a teaching which reads on the instant claimed process. For this reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments with respect to claims **1-41** have been considered but are moot in view of the new grounds of rejection.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Gary Geist, can be reached at (703)-308-1701.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

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L. Eric Crane
Patent Examiner
Group 1600